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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
Biostatistics Branch (HFM-215)

Statistical Review Memorandum

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SPONSOR: *IDEC Pharmaceuticals Corporation*

DATE: *November 15, 1997*

FROM: *Jawahar Tiwari, Ph.D.*

THROUGH: *Peter A. Lachenbruch, Ph.D., Chief*

SUBJECT: *C2B8 (Rituximab, [redacted] antibody) for the treatment of patients with relapsed low-grade or follicular B-cell lymphoma.*
Submission dated February 28, 1997

TO: *Terrye Zaremba, Ph. D.*
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CC: HFM-99/Document Control Center: PLA: 97-0260
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BACKGROUND

The analyses and results presented in this review have been discussed in many meeting with Drs. Patricia Keegan and Bernard Parker.

The efficacy of C2B8 in this submission is based on the results from two studies: 102-02 and 102-05.

Study 102-02

This was a Phase 2 supportive trial enrolling a total of 37 patients with relapsed low-grade or

follicular lymphoma. The dose level selected for this study was 375 mg/m^2 C2B8 once weekly x four. The study was conducted at seven centers in the United States. Patients served as their own control.

Study 102-05

This Phase 3 pivotal trial was an open-label, single-arm, multicenter (31 sites in the United States and Canada) study to evaluate the safety and efficacy of C2B8 in patients with low-grade or follicular non-Hodgkin's lymphoma (Working Formulation A, B, C, or D). A total of 166 patients with relapsed disease (up to four relapses) or failed primary therapy were studied in this trial. All enrolled patients also had progressive disease requiring treatment. Patients with lesions >10 cm were to be excluded. The dose selected for this trial was 375 mg/m^2 C2B8 once weekly times four.

- The primary efficacy variable was specified as overall response to C2B8 (i.e., CR+PR).

- The protocol also defined two important secondary efficacy variables: time to progression for responders and the duration of response.

  ⇨ The ***time to progression*** was measured from the date of first C2B8 infusion to the earliest of the following two dates: date of PD (Progressive Disease) or date of last contact.

  ⇨ The ***duration of response*** was measured from the date of the first observation of $\geq$ 50% shrinkage of tumor response to the earliest of the following two dates: date of PD or date of last contact.

In the absence of a randomized trial, the sponsor agreed with CBER (in a pre-pivotal meeting on 11-1-94 with CBER) that the efficacy of C2B8 should show:

1. Overall response rate in the range of 35 to 40%,
2. Time to progression for responders $\geq$ 8 months, and
3. Duration of response $\geq$ 6 months.

It was also agreed that, in addition to study investigators, an independent panel of experts would evaluate CT scans and classify response as CR (complete response), PR (partial response), SD (stable disease), and PD (progressive disease). The criteria for these response categories were defined in the protocol.

COMMENTS

1. The Primary Efficacy Variable: Overall Response (CR+PR)

The observed CR, PR, and the overall response (CR+PR) from in both studies are given in Table. In the pivotal trial (study 102-05) the overall response rate is 48%, slightly higher than the protocol-specified target response rate of 35 to 40%. In fact, the lower limit of the 95% confidence interval also meets the prespecified requirement for efficacy of this product. The overall response rates in the Phase 2 trial (study 102-02) are very similar and support the results from the pivotal trial. The number of patients in each response category is given in Table 2.

Table 1. The observed number of clinical responses.

STUDY NUMBER	N	Number of Patients With CR (%)	Number of Patients With PR (%)	Number of Patients With CR+PR (%)	95% CI* for CR+PR
102-05	166	10 (6)	70 (42)	80 (48)	(40%, 56%)
102-02	37	3 (8)	14 (38)	17 (46)	(30%, 63%)

* Exact Confidence Interval (StatXact Software)

Table 2. Number of patients in each response category at the time of original submission and 120-day update.

	Best Response	Original Submission		120-Day Update*	
		Response Ongoing	Disease Progression	Response Ongoing	Disease Progression
Responded (CR+PR)	80	56	24	38	42
Stable Disease	70	17	53	12	58
Progressive Disease	11	-	11	-	11
Discontinued**	5	-	5	-	5
Total	166	166		166	

* includes additional five months of follow-up
** Patients did not complete all four infusions

2. Response Evaluation by Study Investigators and an Independent Panel of Experts

A total of 80 patients were classified as responders (Table 1) by the expert panel. In 77 of these 80 patients, the study investigator also classified the patient as responder giving a concordance rate of 96.2% (77/80).

As the data in Table 3 show, a total of 90 patients were classified as responders by the study investigators. In 77 of these 90 patients the LEXCOR panel also classified the patients as responders giving a concordance rate of 85.6% (77/90). The estimate of *Kappa* statistics (a measure of agreement) is 0.84 (95% CI= .76, .92).

Table 3. Response Evaluation: Measure of agreement between investigators and the LEXCOR panel.

		Classification by LEXCOR		
		Responder	*Non-responder*	***Total***
Classification by Investigators	*Responder*	77	13	90
	Non-responder	0	76	76
	Total	77	89	166

Kappa = 0.84 (95% CI = 0.76, 0 .92)

P < 0.0001

3. Time to Progression and Duration of Response

In study 102-05, the observed median time to disease progression and the median duration of response after five months of patient follow-up were 11.8+ and 9.2+ months, respectively (Table 4). These values are higher than the protocol stated and agreed upon "targets" for these efficacy variables. The data from the Phase 2 study are also consistent with these results (Table 4).

Table 4. Time to progression and duration of response in responders in the updated report (based on 120-day patient update).

STUDY NUMBER	Time to Progression (months)			Duration of Response (months)		
	Median	Minimum	Maximum	Median	Minimum	Maximum
102-05 *(N=80)** 120-Day Update**	11.8+	3.6	20.5+	9.2+	1.9	18.8+
102-02 *(N=17)** Original Submission	10.2	4.2	27.9+	8.6	2.6	26.2+

* Total number of responders (CR+PR)
** includes additional five months of follow-up

4. Consistency of Response Across Study Centers

In an attempt to examine the consistency of the response, the number of responders from centers enrolling at least 5 patients were tabulated (Table 5). The observed response rates in 16 such centers ranged from 16.7% to 66.7%. (The response rate based on all 166 patients in the trial is 48.2%.) These numbers do not indicate any unusual pattern suggestive of bias (e.g., indication that the overall response rate observed in the trial is driven by only a few centers).

Table 5. Clinical Response at Sites with enrollment of $\geq$ 5 patients.

Study Site	Total Number of Patients Enrolled	Total Number of Responders (%)
ALL	166	80 (48.2)
1	7	3 (42.9)
3	5	3 (60.0)
5	5	3 (60.0)
6	9	6 (66.7)
7	8	5 (62.5)
8	8	4 (50.0)
9	5	1 (20.0)
11	12	8 (66.7)
14	23	11 (47.8)
16	5	2 (40.0)
17	6	1 (16.7)
18	5	2 (40.0)
20	11	4 (36.4)
22	6	3 (50.0)
32	5	2 (20.0)
41	8	5 (62.5)

5. Baseline Variables Associated with Clinical Response

The patient characteristics at baseline showing significant association with clinical response are given in Table 6. In this analysis, age, gender, histologic grade (low vs intermediate grade: A-C vs D), years since diagnosis, bulky disease, β-2 microglobulin, elevated LDH values, IgM, extranodal disease, and number of prior chemotherapy courses were not associated with the clinical response.

Table 6. Prognostic factors significantly associated with the clinical response

Prognostic Factor at Baseline	Category	Responder	Nonresponder	P-value*
Histologic Type	Type A Type B, C or D	4 (12%) 75 (58%)	29 (88%) 55 (42%)	<0.001
Prior ABMT	Yes No	18 (78%) 62 (43%)	5 (22%) 81 (57%)	0.003
bcl-2 (PB)	Positive Negative	42 (60%) 38 (40%)	28 (40%) 57 (60%)	0.01
bcl-2 (BM)	Positive Negative	41 (58%) 36 (41%)	30 (42%) 52 (59%)	0.04
Bone Marrow Involvement	Yes No	36 (40%) 43 (59%)	54 (60%) 30 (41%)	0.02

* Fisher's Exact Test

6. Response Rate and Prior Chemotherapy

Table 7 provides the results on overall response rate, complete response rate, and the duration of response in patients treated with various courses of chemotherapy. There was no significant association between the prior chemotherapeutic regimens and the clinical response.

Table 7. Duration of response based on the number of previous chemotherapeutic courses.

Prior Chemo Tx Courses	Overall Response Rate	Complete Response Rate	Median Duration of Response (months)
0	40% (2/5)	0% (0/5)	8.6+
1	59% (30/51)	8% (4/51)	9.1+
2	31% (11/36)	6% (2/36)	9.8+
3	49% (24/49)	4% (2/49)	8.1+
≥ 4	52% (13/25)	8% (2/25)	9.2+
All	48% (80/166)	6% (10/166)	9.2+

CONCLUSION

This study was designed as a single arm trial with three prospectively defined (in discussion with CBER) criteria for demonstrating the efficacy of C2B8 (given at a dose of 375 mg/m^2 IV for four doses) in the treatment of patients with relapsed low-grade or follicular B-cell non-Hodgkin's lymphoma. The trial data show that:

- the observed overall response rate was 48% (95%CI: 40, 56),
- the median time to progression was 11.8+ months, and
- the duration response was 9.2+ months.

These results exceed the requirements prospectively established in the protocol.

2. The data from a small Phase 2 trial support these efficacy results.

3. The clinical response evaluated by the study investigators and later on by an independent panel of experts showed good agreement.

4. The data also indicate that the overall response rate for the intent-to-treat population was not driven by only a few study centers.